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POSTGRADUATE COURSE

May 7-8, 2011
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ANNUAL MEETING

May 7-10, 2011
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SOCIETY PUBLICATIONS

Gastroenterology
Editor: Anil K. Rustgi, MD
*Clinical Gastroenterology
and Hepatology*
Editor: C. Mel Wilcox, MD

August 16, 2010

Fred May, MD
Medical Director
Blue Cross Blue Shield of Mississippi
3545 Lakeland Drive
Flowood, MS 39232

Dear Dr. May,

The American Gastroenterological Association is the trusted voice of the GI community. Founded in 1897, the AGA has grown to include 17,000 members from around the globe who are involved in all aspects of the science, practice and advancement of gastroenterology. The AGA Institute administers the practice, research and educational programs of the organization.

The AGA Institute has been contacted by a number of our members who practice in Mississippi who have expressed concern regarding the Blue Cross Blue Shield of Mississippi (BCBS MS) medical policy on **Gastric Electrical Stimulation**. Your current policy decision states, "Gastric electrical stimulation is considered **investigational** for the treatment of gastroparesis of diabetic or idiopathic etiology." We strongly believe that the peer-reviewed literature available on this topic adequately supports that GES is medically necessary for patients that fit the diagnostic criteria of chronic refractory gastroparesis with diabetic or idiopathic etiology.

AGA Education, Practice and Research

Gastroparesis is a chronic disorder of gastric motility characterized by delayed emptying of a solid meal in the absence of mechanical obstruction. The symptoms include early satiety, bloating, distension, abdominal pain, nausea, and vomiting. Postprandial vomiting (1–3 hours after meals) of undigested food is typical. The symptoms of gastroparesis are nonspecific and may mimic other conditions such as ulcer disease, partial gastric or small bowel obstruction, gastric cancer, gallbladder or pancreatic disorders. When severe and chronic, gastroparesis can be associated with dehydration, poor nutritional status, and poor glycemic control in diabetics. Patients with severe gastroparesis vomit constantly, and often become malnourished as a result. While most commonly associated with diabetes, idiopathic gastroparesis is the second most common type of gastroparesis. Gastroparesis is also found in chronic pseudo-obstruction, connective tissue disorders, Parkinson disease, post-surgical and psychological pathology.^{1 2}

Gastroparesis is a relatively rare illness. Primary medical management for gastroparesis includes dietary modification, and pharmacologic therapy with prokinetic and antiemetic agents. Treatment may involve changing or combining medications. Some patients, however, remain refractory to gastroparesis treatment, and are difficult to manage. Patients who fail medical therapies may require placement of a gastrostomy or jejunostomy tube for enteral feedings, or in severe cases, total parenteral nutrition (TPN), although this is not a long-term solution due to the high risk of infection and potentially dangerous side-effects. Patients with medically refractory gastroparesis often have no alternative other than implantation with a device known as gastric electrical stimulation (GES).

Currently, there is only one gastric electrical stimulator that has received approval from the U.S. Food and Drug Administration (FDA). The Enterra™ Therapy System (formerly named Gastric Electrical Stimulation (GES) System), manufactured by Medtronic, is approved for treatment of chronic refractory gastroparesis. GES was granted a humanitarian device exemption (HDE) by the FDA on March 31, 2000, stating that “this device is indicated for the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.” The application must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market, see 21 U.S.C. § 360j. HDEs are granted only

for devices that are expected to be utilized fewer than 4,000 times per year. *Id.* Because they are used to treat rare diseases, large-scale controlled studies are difficult, if not impossible, to conduct. A humanitarian use device may only be used in facilities that have an Institutional Review Board (IRB) to supervise clinical testing of the device.³

As such, when devices with HDEs are released on the market, payers often take the position that they are experimental or investigational. Thus, five years ago, many insurers, including, for example, United Healthcare and Coventry, declined to cover GES. Today, these and other insurers, including Regence BlueCross BlueShield, Cigna, Wellcare, BlueCross BlueShield of Minnesota, Aetna, Anthem BlueCross BlueShield, BlueCross BlueShield of Vermont, Independence BlueCross, Premera BlueCross, Highmark BlueCross Blue Shield, Humana, Horizon BlueCross and BlueShield of New Jersey, BlueCross BlueShield of Florida, BlueCross BlueShield of Alabama, Health Care Service Corporation (dba Blue Cross and Blue Shield of Texas, Illinois, New Mexico and Oklahoma) , HealthNet, Medical Mutual of Ohio, Emblem Health, and Medicare cover GES routinely in patients whose gastroparesis has proven to be refractory to other treatments.

The Enterra Therapy system is composed of a neurostimulator, an implantable intramuscular lead and an external programming system. The system uses the implanted neurostimulator to deliver electrical impulses to nerves in the stomach. The electrical stimulation produced by this device stimulates the stomach to contract and helps control the symptoms associated with gastroparesis, including nausea and vomiting. The data presented to the FDA documenting the "probable benefit" of the GES (Enterra™) system was based on a multicenter double-blind cross-over study referred to as the WAVESS study (Worldwide Anti-Vomiting Electrical Stimulation Study).⁴ The study included 33 patients with intractable idiopathic or diabetic gastroparesis. The primary endpoint of the study was a reduction in vomiting frequency, as measured by patient diaries. Abell, et al. (2003) reported on a two phase clinical study of GES for gastroparesis: in the first phase, lasting 2 months, the investigators attempted to blind participants to stimulation. In the first phase, 33 patients with gastroparesis (17 diabetic, 16 idiopathic) were randomized to stimulation either ON or OFF for 1 month, then crossed over to the other mode for 1 month. During the second uncontrolled phase of the study, all patients had their stimulator turned ON and were followed at 6 and 12 months. The investigators reported that, during the first phase of the study, vomiting frequency was significantly less in the ON position, than in the off position, with weekly vomiting frequencies of 6.8 and 13.5 episodes, respectively ($p < 0.05$). Total symptom score (mean sum of 6 symptoms, rated from 0 (absent) to 4 (severe) was also slightly less in the ON position than the OFF position,

with scores of 12.5 + 1.0 and 13.9 + 1.1, respectively. The investigators noted that 21 patients preferred the ON mode and 7 patients preferred the OFF mode.

In a continuing open phase of the trial, the patients then received the stimulation consistent with their preference. However by 4 months all patients had the device turned ON (it is not clear whether this phase was by preference or design). At 6 and 12 months' follow-up, the mean number of vomiting episodes continued to decline, although only 15 patients were followed for a period of 12 months. Data regarding quality of life were also obtained at 6 and 12 months and showed improvement. At 6 months, there was a significant improvement in 2-hour gastric retention (from 80% retention to 60% retention), but not in 4-hour gastric retention. (Fifty percent gastric retention at 2 hours is considered the upper limits of normal.)

In an update to the WAVESS double-blind study, Abell and colleagues reported twelve months outcomes for all of the patients.⁵ Statistically significant improvements were found for weekly vomiting frequency, total abdominal symptom score, and scintigraphic solid food emptying. At baseline the median vomiting frequency was 17.3 episodes per week with gastroparetic symptoms over a mean 6.2 years. All patients had scintigraphic evidence of delayed gastric emptying at two and four hours, all patients were refractory to prokinetic and antiemetic medications, and fourteen required some form of parenteral or enteral feedings. Results at the end of phase 1 (the blinded phase) showed a 50% decreased vomiting frequency for patients whose devices were in the ON compared to patients whose devices were in the OFF positions ($p=0.05$). Symptom severity trended toward improvement in the ON versus OFF period, although these changes did not reach statistical significance in phase 1. Before unblinding, twenty-one patients expressed preference for the ON position. In a second phase of the study all patients were switched to the ON position with six and twelve months follow-up. Vomiting results at twelve months significantly decreased compared to baseline: 72% for the combined group, 63% for diabetics with gastroparesis and 83% for patients with idiopathic gastroparesis. Total symptom score improved significantly ($p<0.05$) at six and twelve months. Physical and mental quality of life scores improved significantly compared to baseline ($p=$ less than 0.025). Baseline gastric retention was 78% at two hours. This decreased significantly with electrical stimulation to 65% at six months and 56% at twelve months for the combined group. Four-hour gastric emptying improved from 34% retention at baseline to 22% retention at twelve months. The difference was statistically significant for the combined group as well as the diabetic and idiopathic groups separately.

Abell and colleagues published five-year outcomes in a subset of twelve patients from the Gastric Electro-Mechanical Stimulation (GEMS) Study Group.⁶ In this subgroup of

twelve, baseline total symptom score changed from 37.1 to 15.8 at one to two years and to 20.3 at five years ($p < 0.005$). Weekly vomiting frequency score decreased from 3.9 at baseline to 1.4 at one to two years and 1.7 at five years. Route of nutrition changed also: at five years nine patients were taking oral nutrition representing a 30% change from baseline from enteral or parenteral nutrition to oral foods alone.

Forster and colleagues reported on their experience at a single institution among 55 patients with gastroparesis as documented by gastric retention.⁷ While the total symptom score improved, gastric emptying did not change. Similarly, van der Voort and colleagues reported that seventeen patients with diabetic gastroparesis experienced a decrease in nausea and vomiting and an improvement in glucose control in a prospective case series examining the twelve month outcomes.⁸ McCallum, et al. reported on 12 month outcomes of GES in an uncontrolled study of a small group ($n = 16$) of subjects with post-surgical gastroparesis.⁹ The investigators reported that, after application of GES, there was significant improvement in upper gastrointestinal symptoms, quality of life, nutritional status, and hospitalization requirements. Lin and colleagues reported significant improvements in upper GI symptoms, health-related quality of life, nutritional status, glucose control, and hospitalizations at six and twelve months in a retrospective review of 48 adult patients with diabetes who received a gastric electrical stimulation implant.¹⁰ The review also noted that gastric emptying was not significantly faster. The authors subsequently reported intention-to-treat analysis of these patients at a follow-up of 45 months.¹¹ The improvements reported at 12 months follow-up were sustained beyond three years. Mason and colleagues reported on the 20-month follow-up of 27 of 29 patients referred for gastrectomy who instead received GES for refractory gastroparesis.¹² Three patients required additional procedures due to poor outcomes. Nutritional support was discontinued in the 19 patients who were dependent on supplemental feeding prior to the procedure. Gastric emptying rates also improved.

O'Grady et al. performed a meta-analysis of 13 studies evaluating GES for the treatment of medically refractory gastroparesis.¹³ Uncontrolled observational studies ($n=12$) and one blinded randomized control trial (RCT) were included. The findings reported from this review were that following GES, patients had statistically significant improvements in total symptom severity score ($p=0.01$), vomiting severity score ($p < 0.0001$), and nausea severity score ($p < 0.0001$).

Based on the literature, the AGA recommends that gastric electrical stimulation may be considered medically necessary in the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology when there is:

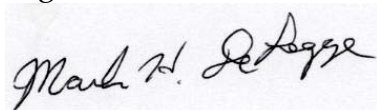
1. Significantly disordered gastric emptying as documented by wireless capsule measurement of gastric emptying or scintigraphic imaging of solid food;
2. Patient is refractory or intolerant to prokinetic and antiemetic medications; and
3. Patient has malnutrition as documented by formal nutritional assessment

The available intermediate and long-term data indicate that gastric electrical stimulation may be associated with improvements in gastrointestinal symptom scores, nutrition and quality-of-life for patients with gastroparesis of diabetic or idiopathic origin and that these improvements are sustained over time. Therefore, we recommend that BCBS MS review this policy and reconsider the current policy decision based on the current medical literature.

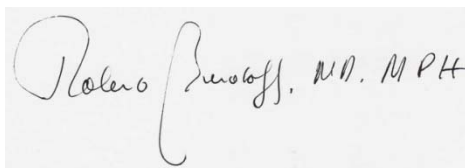
In addition, we have learned from our members in Mississippi that BCBS MS not only refuses to undertake individualized consideration of requests for coverage of GES, but refuses to conduct prior authorizations or pre-service reviews of requests for coverage of GES, unlike nearly every other insurer in the United States. Thus, patients are deprived of a meaningful opportunity to appeal a noncoverage decision before the device is implanted. Instead, they must take the risk that they will be unable to obtain insurance coverage of the device, and that they will have to pay for the device and surgery themselves. We strongly urge you to revisit this process and develop a mechanism for physicians and their patients to submit and receive prior authorization for a GES procedure.

We appreciate the opportunity to comment on this policy decision. If we may provide any additional information, or if you would like to discuss this matter, please contact Adam Borden, MHA, Manager, New Technologies and Reimbursement, AGA, at 301-941-2629 or aborden@gastro.org. Thank you.

Regards,



Mark H. DeLegge, MD, AGAF
Chair, AGA Institute Practice Management and Economics Committee



Robert Burakoff, MD, MPH, AGAF
Chair, AGA Public Affairs and Advocacy Committee



John M. Inadomi, MD, AGAF
Chair, AGA Institute Clinical Practice and Quality Management Committee

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¹² Mason RJ, Lipham J, Eckerling G et al. Gastric electrical stimulation: an alternative surgical therapy for patients with gastroparesis. *Arch Surg* 2005;140(9):841-6.

¹³ O'Grady G, Egbuji JU, Du P, Cheng LK, Pullan AJ, Windsor JA. High-frequency gastric electrical stimulation for the treatment of gastroparesis: a meta-analysis. *World J Surg*. 2009 Aug;33(8):1693-701.